Exhibit 196

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RESTRICTED CONFIDENTIAL

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE

IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	MDL No. 2875

EXPERT REPORT OF ERIC SHEININ, PH.D.

I. INTRODUCTION

1. My name is Eric Sheinin, Ph.D. I am a regulatory specialist and organic chemist with substantial experience in the regulatory process at the United States Food and Drug Administration ("FDA"). I submit this expert opinion on behalf of Mylan Laboratories Ltd. and Mylan Pharmaceuticals Inc. in connection with the above-captioned litigation.

2. I reserve the right to amend or supplement my opinions in light of evidence presented by Plaintiffs or additional information that may be made available to me in the future. I also reserve the right to convey my opinions through the use of demonstrative exhibits at trial.

3. If called upon, I am prepared to testify about my background, qualifications, experience, and the issues and opinions described in this Report. Furthermore, I anticipate that I may be asked to provide testimony and to consider and respond to arguments that Plaintiffs' expert(s) or fact witnesses may raise at any hearing, in reports, and/or at trial.

4. I am being compensated for my time in connection with this matter at a rate of $575/hour for consulting, deposition, or expert witness testimony. Non-productive travel time is

invoiced at $288/hour. My compensation is not dependent on the outcome of this matter in any way.

5. I have testified as an expert witness at deposition or trial in the past four years in the following matter: Hospira, Inc v Fresenius Kabi USA, LLC, United States District Court for the Northern District of Illinois (deposition).

6. A copy of my most current CV is attached hereto as Exhibit A.

7. A list of materials provided for my consideration is attached as Exhibit B.

8. I offer the opinions set forth in this Report to a reasonable degree of scientific certainty based on my education, experience, training, expertise, and referenced resources.

II. PERSONAL BACKGROUND AND QUALIFICATIONS

9. I am a regulatory professional and an organic chemist with over 50 years of experience including 30 years of experience in various roles at the U.S. Food and Drug Administration ("FDA"), 6 years of experience in various roles at the United States Pharmacopeial Convention, Inc. ("USPC"), and nearly 15 years as a consultant to the pharmaceutical industry, advising clients in the areas of regulatory affairs and chemistry, manufacturing, and controls ("CMC") area, as well as in issues related to the United States Pharmacopeia "("USP") and National Formulary ("NF"). The following is a summary of my background and qualifications as set out in my curriculum vitae, a copy of which is attached as Exhibit A to this report.

10. I received my undergraduate and graduate training at the University of Illinois. In 1965, I received my Bachelor of Science in zoology from the University of Illinois, Urbana-Champaign, Illinois. After one year at the University of Illinois College of Pharmacy at the medical center in Chicago, Illinois, I entered graduate school in the Medicinal Chemistry

department at the College of Pharmacy. I completed my Ph.D. training and dissertation and received my degree in June 1971 majoring in organic chemistry.

11. Upon completing my training, I began a 30 year career at the FDA. During my first 14+ years I worked as a research and supervisory chemist in the Division of Drug Chemistry, Bureau of Drugs (the predecessor of the Center for Drug Evaluation and Research ("CDER")). My area of research involved the use of nuclear magnetic resonance spectroscopy and mass spectrometry to develop analytical methods of drug analysis and to identify unknown samples. When a supervisory position became vacant I was selected to lead the Drug Standards Research Branch where the laboratory chemists working for me were responsible for validating the analytical methodology included in new drug applications ("NDA") and abbreviated new drug applications ("ANDA"), research utilizing X-ray powder diffraction, and the evaluation of proposed USP Official Reference Standards.

12. In approximately 1985, the Bureau of Drugs and the Bureau of Biologics merged, which led to the eventual closing of the Division of Drug Chemistry in the interest of adding additional personnel to the chemistry review of NDAs. At that time, I moved to the Division of Oncology and Radiopharmaceutical Drug Products as a Supervisory Chemist, one of 6 clinical review divisions at that time in CDER, where my subordinates were responsible for anti-inflammatory drug products. In this position I was responsible for directing the activities of review chemists responsible for the CMC portions of investigational new drug applications ("IND"), amendments and annual reports to these applications and NDAs as well as supplemental NDAs and annual reports to these applications. Within the first year in this position I also assumed responsibility for the review chemists working on the oncology and

radiopharmaceutical drug products. The latter ultimately also encompassed drugs intended for increased visualization in magnetic resonance imaging and ultrasound.

13. Over the ensuing 10 years and after a series of reorganizations, I had responsibility for other categories of NDAs such as surgical/parenteral drug products, ophthalmic drug products, dermatology drug products, and dental drug products.

14. In 1995, a major reorganization in CDER created the Office of Pharmaceutical Science ("OPS") with 4 smaller offices within it including the Office of New Drug Chemistry ("ONDC"). Within the ONDC, 3 Divisions of New Drug Chemistry ("DNDC") were created and I was selected to lead DNDC3. In 1996, I was selected to the position of Director of ONDC. In this position I was responsible for the activities of all the review chemists and review microbiologists in the new drug area as well as the support staff numbering approximately 110 in total.

15. In 1999 I moved up to the OPS immediate office as the deputy director for science. In this position, I interacted closely with the directors of the 4 offices within OPS assisting the OPS director in the day to day operations.

16. During my 15+ years in the review area, I interacted closely with counterparts in the Office of Generic Drugs ("OGD") working to harmonize the CMC requirements for NDAs and ANDAs as well as to create Guidances for Industry which provided the pharmaceutical industry the best thinking of CDER, the Center for Biologics ("CBER") and the Center for Veterinary Medicine ("CVM") in areas of mutual interest and responsibility. Many of these guidances are still in effect today and some have been updated.

17. I was also frequently invited to present at scientific seminars and conferences. I also represented FDA both domestically and internationally. For instance, I was involved in

developing guidelines produced by the International Council (formerly Conference) on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ("ICH"). I was a member of the expert working groups for the Q2A and Q2B guidelines, since combined into Q2, which pertained to the validation of analytical methodology. I also was the rapporteur for the Q6A guideline on setting specifications for new drug substances and new drug products. In addition, I worked on guidelines for impurities in drug substances, Q3A, drug product, Q3B, and residual solvents, Q3C.

18. Upon retiring from the FDA, I joined the USPC as a vice president responsible for supervising the USPC scientists who interacted with the industry providing information for the creation of the content of the USP and the NF along with the volunteers on Expert Committees who made decisions on when that content was ready to become official in the USP and the NF. I also was involved in the launch of the USPC program for the verification of the quality of pharmaceutical ingredients used in drug products marketed in the U.S. In addition, I was the USPC lead at the Pharmacopeial Discussion Group where representative of the USPC, the European Pharmacopoeia, and the Japanese Pharmacopoeia interacted to harmonize various excipient monographs and general chapters.

19. After 6 years at the USPC, I retired and entered consulting as president of Sheinin & Associates LLC where I consult with the pharmaceutical industry. During the past 14+ years I have worked with companies with pending ANDAs and NDAs and supplements as well as INDs, reviewing proposed material for submission to the FDA, and assisting them with responses to various types of requests for additional information. I have performed due diligence on pre-IND and IND and NDA information and reviewed and commented on the adequacy of drug master

files ("DMF"). My consulting has involved solid and liquid oral dosage forms, injectable products, and drug-device combination products.

20. Over the course of my career I also have provided training on FDA issues related to the CMC portion of applications and on USP requirements.

21. I am an emeritus member of the American Chemical Society and a fellow of the American Association of Pharmaceutical Scientists ("AAPS").I currently am a member of the USP Nomenclature and Labeling Expert Committee.

22. I am the author or co-author of approximately 40 scientific publications in such journals as Pharmaceutical Research, American Pharmaceutical Review, Journal of Organic Chemistry, and the AAPS Journal.

23. I have been a lecturer on a variety of topics related to regulatory and CMC issues in pharmaceutical development and have delivered more than 200 presentations at national and international scientific conferences, symposia, and internal and external programs.

24. I taught freshmen chemistry at Montgomery College in Rockville, Maryland for 16 years while working at the FDA.

III. OVERVIEW OF REGULATORY PRINCIPLES APPLYING TO THE MANUFACTURE OF DRUG SUBSTANCES AND DRUG PRODUCTS

a. Submission of DMFs and Related Review in the Context of NDA/ANDA Submissions

25. NDA and ANDA applicants are responsible for all of the information contained in an application including all of the CMC information. Often other companies are involved in various portions of the CMC information, e.g., supply of ingredients used in the manufacture of the drug substance or the drug product, supply packaging materials, and even manufacture of the drug substance.

26. A Drug Master File ("DMF") provides a mechanism for suppliers and contractors to an applicant to provide confidential information to the FDA without revealing this information to the applicant. For example, the applicant may purchase the drug substance from a contractor and the contractor wishes to maintain confidentiality. As FDA requires this information for its review, the contractor then is able to provide all of the chemistry, manufacturing, and controls information for that drug substance to a Drug Master File.

27. DMF holders can file a DMF at any time but FDA will not review the DMF until there is an application that references that DMF.

28. DMF holders must authorize their customers to reference their DMFs by providing a letter to their customers detailing the name of the company authorized to reference the DMF, the date of the authorization, and the date of the submission to their DMF. This letter must then be presented to the FDA as part of the NDA or ANDA application.

29. There are 4 types of DMFs;

Type II – drug substances, drug substance intermediates, and materials used in their preparation, or drug product

Type III – Packaging material

Type IV – Excipient, colorant, flavor, essence, or material used in their preparation

Type V – FDA accepted reference information

30. DMFs are discussed in the regulations at 21 CFR 314.420 for drugs and at 21 CFR 601.51(a) for biologics licensing applications ("BLA").

31. DMFs are neither approved nor disapproved; rather any deficiencies are reported to the DMF holder and the FDA will inform the ANDA or NDA applicant that information from

the DMF holder has been requested. Generally, if there are outstanding issues with a given DMF, the application that is allowed to reference that DMF cannot be approved. The applicant is responsible for everything in the submission.

32. DMFs also are used to provide confidential information in support of Investigational New Drug Applications("INDs").

b. Role of USPC in Establishing Standards and Specifications

33. The USP predates the establishment of the U.S. Food and Drug Administration (FDA).

34. The American Pharmaceutical Association published the first National Formulary ("NF") as The National Formulary of Unofficial Preparations. USPC acquired the NF in 1975 and began publishing the two compendia in a single volume. The NF contains monographs for excipients used in the manufacture of drug products. Some NF ingredients also are drug substances, e.g., mannitol.

35. The USPC is a private, nongovernmental, nonprofit corporation that establishes standards, included in USP-NF, for pharmaceuticals and other articles legally marketed in the United States. Its standards are enforced by the FDA. The legal standing of the USP and the NF arises through the Federal Food, Drug, and Cosmetic Act (The Act) of 1906 and its amendments.

36. Section 201 [321] of The Act reads, (1)The term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any

function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C).

37. Thus, drug substances, drug products, and excipients fall within the definition of a "drug".

38. Section 201 [321] reads, (j)The term "official compendium" means the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, official National Formulary, or any supplement to any of them.

39. The Act 501 [351] (b) states that a drug or device shall be deemed to be adulterated if it purports to be or is represented in an official compendium, and its strength differs from, or its quality or purity falls below, the standard set forth in such compendium. Such determination as to strength, quality, or purity shall be made in accordance with the tests or methods of assay set forth in such compendium.

40. Thus, if there is a USP monograph for a given drug, an ANDA must meet the requirements set forth in that monograph in order for FDA to approve that application.

41. With some exceptions where a revision to a given monograph is necessary, the USPC publishes for public comment all proposed revisions to the USP-NF in its bimonthly journal Pharmacopeial Forum ("PF"). Revisions include proposals for either new or revised monographs, general chapters, or miscellaneous information. The process begins with the submission of a proposal for revision. Requests for revision must be submitted in accordance with the USP Guideline for Submitting Requests for to Develop or Revise USP-NF Standards.

42. All requests for revision are assigned to one of the USP's scientific liaisons for review. The liaison evaluates the relevancy. supportability, and urgency of the request in accordance with established policies and procedures. The liaison may contact the sponsor and

request additional information or clarification if the information provided is incomplete or the liaison has any questions. This process is explained in greater detail in the Pharmacopeial Methods and Tests chapter of the textbook, Specifications of Drug Substances and Product by C.M.Riley, T.W. Rosanske, and G. Reid.

43. The liaison may initiate work on the request or submit the request to the relevant Expert Committee for decision or Expert Panel for its recommendations.

44. Once the request is complete the liaison forwards the request for publication in the PF. Interested parties have 90 days to comment on the proposed revision. Any comments received by USP are collated by the scientific liaison and forwarded to the assigned Expert Committee.

45. USP expert committees are responsible for developing and revising USP standards for medicines that appear in the USP and the NF, USP Compounding Compendium, Herbal Medicines Compendium, Dietary Supplements Compendium, and Food Chemicals Codex. They also approve USP Reference Standards.

46. The Expert Committees are each focused on a different area of standards. They develop and review monographs, general chapters, and general test methods. Revisions are adopted by majority vote of the expert committee members.

47. Expert committee members are elected based on their experience and background and come from the pharmaceutical industry, academia, and governments (both domestic and foreign). Members are volunteers and do not represent their companies, universities, or governments.

48. The assigned expert committee reviews and evaluates the comments that were received. If no comments are received or the comments received are deemed minor, the expert

committee members vote to approve the revision (with possible alterations) for official status. Approval may occur through publication in the next edition of USP-NF or one of the two annual supplements, through an Interim Revision Announcement ("IRA") in the PF, or through a revision bulletin that is posted on the USP website.

49. IRAs are published in PF for the 90-day comment period. If there are no significant comments, the IRA becomes official in the "Official Text" section of the USP Web site, with the official date indicated. Revision bulletins are used when circumstances require rapid publication of official text. Revision Bulletins are posted on the USP website with the official date indicated.

50. Regardless of the route, the responses and comments are always posted on the USP website. If the expert committee determines that the comments are significant the request for revision may be republished for public comment in the PF. The comments and responses are then included with the revision proposal in the PF.

51. Per Section 501(b) of the FDCA, the USP and the NF are both recognized as legal standards for drugs marketed in the United States. USP and FDA work together in a number of ways. If there is a USP monograph, any article to be marketed in the U.S. must meet that monograph unless the reason it does not is indicated in the labeling. This applies whether the article is labeled USP or not.

52. Numerous FDA staff members participate as government liaisons on USP's Expert Committees and Expert Panels, the scientific bodies that develop and revise USP's written and physical standards. Government liaisons represent FDA opinions and viewpoints (as opposed to other USP volunteers, who represent their own opinions rather than their employers')

at public USP meetings such as the Expert Committee Meetings, Expert Panels and Stakeholder Forums.

53. USP provides comments on FDA Federal Register notices and co-sponsors workshops with FDA on pertinent topics.

54. USP and NF monographs include information on packaging and storage as well any labeling requirements. All articles in USP or NF are subject to the packaging and storage requirements specified in General Chapter Packaging and Storage Requirements ⟨659⟩, unless different requirements are provided in an individual monograph. All articles in USP or NF are subject to the labeling requirements specified in General Chapter Labeling ⟨7⟩, unless different requirements are provided in an individual monograph.

55. In most instances USP monographs are in agreement with the approved NDA/ANDA specification. FDA cannot provide information in their comments that is confidential. Thus, specific information cannot be provided to USP to help create new content. However, if a PF proposal for a new drug substance or drug product monograph includes an impurity procedure that is not in any approved application, neither NDA nor ANDA, FDA could indicate that the proposed impurity procedure is not used in any approved application without revealing any confidential information.

56. Typical USP drug substance and drug product monographs include Universal Tests; description, identification, assay, and impurities. The description of the drug substance is not included in the actual monograph but appears in a reference table – Description and Solubility. This table is not intended to replace, nor should it be interpreted as replacing, the definitive requirements stated in the individual monographs. For example, the description for amlodipine besylate reads, “A white or almost white powder. Freely soluble in methanol;

sparingly soluble in alcohol; slightly soluble in 2-propanol and in water." USP drug product monographs do not include a description. However, a description of the drug product is required to be included in the NDA or ANDA application.

57. USP monographs also include a varying number of Specific Tests that depend on what type of drug the drug substance will be used in and for drug products, the type of dosage form. For example, the USP monograph for Valsartan Tablets includes tests for dissolution and uniformity of dosage units.

IV. DRUG SUBSTANCE IS TO BE MANUFACTURED IN ACCORDANCE WITH THE STANDARDS AND SPECIFICATIONS SET FORTH IN THE DMF AND THE USP MONOGRAPH

58. Under federal law, APIs are to be manufactured in accordance with the information included in the DMF or in the NDA or ANDA application. Some NDAs and ANDAs do not reference a DMF as the applicants manufacture the API in-house. Some NDA and ANDA applicants purchase the API from another organizational component within the corporate structure and there may or may not be a DMF involved. If there is a DMF, the same principles described above are applicable.

59. Regardless of whether there is a DMF, the API is expected to meet all of the requirements contained in a USP monograph where a monograph appears in the USP.

60. The ICH Q7 guideline Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients provides guidance regarding good manufacturing practice ("GMP") for the manufacturing of APIs under an appropriate system for managing quality. It is also intended to help ensure that APIs meet the requirements for quality and purity that they purport or are represented to possess.

61. In Q7 "manufacturing" is defined to include all operations of receipt of materials, production, packaging, repackaging, labelling, relabeling, quality control, release, storage and distribution of APIs and the related controls. In Q7 the term "should" indicates recommendations that are expected to apply unless shown to be inapplicable or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance

62. Within the world community, materials may vary as to the legal classification as an API. When a material is classified as an API in the region or country in which it is manufactured or used in a drug product, it should be manufactured according to this Q7 guideline. As FDA is a member of ICH, it is expected that APIs used in approved drug products sold in the United States will be manufactured under the GMPs described in Q7.

63. Q7 applies to APIs that are manufactured by chemical synthesis, extraction, cell culture/fermentation, by recovery from natural sources, or by any combination of these processes.

V. MYLAN'S VALSARTAN API MANUFACTURED BETWEEN MARKET ENTRY IN 2012 AND THE RECALLS IN 2018 COMPLIED WITH THE STANDARDS AND SPECIFICATIONS IN PLACE AT THE TIME OF MANUFACTURE

64. According to the USP Valsartan API monograph that was official until April 30, 2020, the last time this monograph appeared in PF, indicating that USP was proposing changes to the monograph, was in PF 33(3). PF 33(3) was the May-June 2007 volume of PF. The proposed change involved a revision to the preparation of the standard solution for test 2 in Related Compounds. There was no mention of nitrosamines in the proposed revision. In fact, the current official Valsartan API monograph does not mention nitrosamine. Test 2 is now Procedure 2 and it includes "any other individual impurity" with an acceptance criteria of not more than 0.1%, multiple times higher than the FDA Acceptable Intake for a given nitrosamine.

65. A new version of the monograph became official on May 1, 2020. The only change from the previous monograph was in Identification test A; Infrared Absorption <197M> was changed to Spectroscopic Identification Test, <197>, Infrared Spectroscopy 197M. Thus, there has been no other changes proposed to the USP Valsartan API since the May-June 2007 volume of PF.

66. Simply put, per the USP monograph, there were no tests or acceptance criteria in place with respect to nitrosamine content or testing aimed at detection of nitrosamine impurities.

67. Similarly, neither Mylan's DMF nor FDA's guidance required manufacturers to control or test specifically for nitrosamine impurities until the origin of FDA's investigation of ARBs in mid-2018.

68. Mylan's Valsartan USP API continued to meet its specification as well as its DMF specification throughout this period.

a. Until the Investigations Were Launched in 2018, Neither FDA Nor USP Had Established a Test and Acceptance Criteria with Respect to Nitrosamine Impurities in Valsartan API.

69. All API and drug products contain impurities. A drug substance or drug product is not considered misbranded or adulterated simply because it contains impurities (even potentially genotoxic impurities).

70. The FDA Guidance for Industry Control of Nitrosamine Impurities in Human Drugs issued in September 2020 states, "The recent unexpected finding of nitrosamine impurities, which are probable human carcinogens, in drugs such as angiotensin II receptor blockers (ARBs), ranitidine, nizatidine, and metformin, has made clear the need for a risk assessment strategy for potential nitrosamines in any pharmaceutical product at risk for their presence."

71. As indicated in its public statements, FDA first learned of the presence of N-nitrosodimethylamine ("NDMA") when Prinston Pharmaceuticals Inc. ("Prinston"), contacted the Agency on June 19, 2018, about its products containing valsartan API manufactured by Zhejiang Huahai Pharmaceutical Co. ("ZHP"). NDMA is a chemical found in water and some foods, including meats, dairy products, and vegetables. The levels of NDMA in ZHP's valsartan API, while still trace amounts, were deemed by FDA to be unacceptable.

72. N-nitrosodiethylamine ("NDEA") also has been reported in ARBs and other APIs and drug products. Additional nitrosamines have been found in some other APIs and drug products. All were unexpected before FDA launched its investigation in mid-2018.

b. Routine Testing Methods for Known and Unknown Impurities Were Not Sufficiently Sensitive and/or Specific to Have Detected NDEA at the Levels Ultimately Found in Mylan's Valsartan USP API.

73. FDA published an update in question and answer format on the recall of ARBs valsartan, losartan, and irbesartan that was current as of February 3, 2021. In discussing the need for a risk analysis of potential nitrosamine impurities FDA concluded, "Before we undertook this analysis, neither regulators nor industry fully understood how the nitrosamines could form during the manufacturing process." By regulators, FDA was referring to itself as well as other regulators around the world. By industry, FDA was referring to the international pharmaceutical community.

74. Once FDA became aware of potential presence of NDMA in valsartan drug products in June 2018, CDER's Office of Technology and Research ("OTR") developed and implemented a combined head space gas chromatography-mass spectrometer/mass spectrometer ("GC-MS/MS") method to quantitate NDMA and NDEA at trace levels.

75. This method is capable of detecting and quantitating the above 2 nitrosamines as well as 2 other nitrosamines that may also be present in valsartan. These are N-nitrosoethylisopropylamine ("NEIPA") and N-nitrosodiisopropylamine ("NDIPA") The method utilizes gas chromatography to separate the 4 nitrosamines from each other and from valsartan and they are detected by a mass spectrometer/mass spectrometer.

76. This method is capable to simultaneously detect and quantitate these 6 nitrosamines in valsartan drug substance and drug product at sub-ppm levels.

77. ICH Q2 defines the detection limit as "The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value." It defines the quantitation limit as, "The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy."

78. The OTR method detection limit for the 6 nitrosamines ranged from 0.05 to 0.32 ng/mL (0.003 to 0.016 parts per million ("ppm")) and the quantitation limit was 1.0 ng/mL (0.05 ppm). The validated range of the method varied from 1.0 - 100 to 1.0 – 200 ng/mL (0.05 – 5.0 to 0.05 - 10.0 ppm).

79. This is not a routine quality control method typically used to monitor and control impurities in drug substances and drug products.

80. Before the emergence of FDA's nitrosamine investigation in mid-2018 and the Agency's and industry's efforts to develop novel methods to identify and quantify nitrosamine impurities at the trace levels detected in Mylan's Valsartan API, the testing performed in accordance with the USP monograph for Valsartan API and Mylan's DMF were not sufficiently sensitive to have detected NDEA at the levels detected in Mylan's Valsartan USP API. [redacted]

[redacted]. In contrast, the highest level of NDEA detected in any batch of Mylan's Valsartan USP API was 1.57 ppm. Conventional testing, such as the High-Performance Liquid Chromatography ("HPLC") methods included in the USP monograph would not have detected an impurity at that level.

81. USP includes a new general chapter titled Nitrosamine Impurities that became official on December 1, 2021. Part of the introduction to this general chapter, in referring to the reported detection of NDMA and NDEA in valsartan, reads, "This observation triggered extensive synthetic route assessments and development of analytical procedures to quantify these two nitrosamine impurities. As additional pharmaceuticals were evaluated and, in some cases tested, other nitrosamines beyond NDMA and NDEA were added as impurities of concern." USP has developed 2 separate analytical procedures to detect and control nitrosamines in valsartan.

82. As of the date of preparation of this expert opinion, I am not aware of any proposals to include revisions to any USP or NF monograph that would include tests and acceptance criteria for specific nitrosamines in drug substance or drug product therein.

VI. RESPONSE TO THE EXPERT DECLARATION OF RON NAJAFI, PH.D.

83. Dr. Najafi states under General Responsibilities of a Drug Company that, "Generic drugs are expected to be the same as the brand name drug, which in the case of Valsartan was Diovan or Exforge". He also states, "It was the drug manufacturers' responsibility to manufacture Valsartan to be the same chemically equivalent and pass the same quality and purity standards as Diovan and/or Exforge."

84. Dr. Najafi continues, "Generic drug manufacturers have an ongoing federal duty of sameness in their products. The generic manufacturer must demonstrate that their active

ingredient(s) are the same as the Reference Listed Drug("RLD") and have identical strength, quality, purity, potency (and where applicable, other characteristics) as the RLD."

85. 21 CFR 314.94(a)(5)(i) reads, "For a single active-ingredient drug product, information to show that the active ingredient is the same as that of the reference single-active-ingredient listed drug, as follows: (A) A statement that the active ingredient of the proposed drug product is the same as that of the reference listed drug."

86. Mylan also markets two combination products: Valsartan/HCT tablets and Amlodipine/Valsartan tablets.

87. 21 CFR 314.94(a)(5)(iii) reads, "For a combination drug product, information to show that the active ingredients are the same as those of the reference listed drug except for any different active ingredient that has been the subject of an approved petition, as follows: (A) A statement that the active ingredients of the proposed drug product are the same as those of the reference listed drug, or if one of the active ingredients differs from one of the active ingredients of the reference listed drug and the ANDA is submitted under the approval of a petition under § 314.93 to vary such active ingredient, information to show that the other active ingredients of the drug product are the same as the other active ingredients of the reference listed drug, information to show that the different active ingredient is an active ingredient of another listed drug or of a drug that does not meet the definition of "new drug" in section 201(p) of the Federal Food, Drug, and Cosmetic Act, and such other information about the different active ingredient that FDA may require.

88. Further, a generic drug must be shown to be bioequivalent to the RLD. 21 CFR 314.94(a)(7)(i) reads, "Information that shows that the drug product is bioequivalent to the reference listed drug upon which the applicant relies."

89. Mylan Laboratories Ltd. manufactures Valsartan USP API pursuant to DMF 018253. ANDA 090483 (amlodipine and valsartan tablets), ANDA 090866 (valsartan tablets), and ANDA 078020 (valsartan and hydrochlorothiazide tablets) incorporated by reference DMF 018253 for the purpose of incorporating Mylan Laboratories Ltd.'s Valsartan USP API as the drug substance in the aforementioned finished-dose drug products.

90. FDA approved ANDA 090866 on January 5, 2015.[1]

91. FDA approved ANDA 078020 on September 21, 2012.[2]

92. FDA approved ANDA 090483 on March 30, 2015.[3]

93. In approving these ANDAs, FDA would have analyzed DMF 018253 and determined that drug product incorporating Mylan Laboratories Ltd.'s Valsartan USP API and manufactured in accordance with the referenced standards and specifications would be considered the same as and bioequivalent to the relevant RLDs for purposes of compliance with the FDCA.

94. The suppliers of a given API used in an ANDA often utilize a synthetic route that differs from that of the supplier of an API used in the RLD. Because the synthetic process differs it is quite common for a different set of impurities to be present in the API used in an ANDA, i.e., there can be a different impurity profile.

95. During the time when I worked at the USP we developed an approach termed the Flexible Monograph. This approach was intended to allow multiple impurity profiles based on the route of synthesis to meet the requirements of the monograph.

[1] https://www.accessdata fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=090866
[2] https://www.accessdata fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=078020
[3] https://www.accessdata fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=090483

96. An example is seen in the Loratidine USP monograph. There are 2 procedures for the control of organic impurities. The monograph states, "On the basis of the synthetic route, perform either Procedure 1 or Procedure 2." Other drug substance monographs contain similar provisions for differing routes of synthesis.

97. The fact that a given API contains a different set of impurities does not in itself mean that it differs from the API used in an RLD. This is an evaluation that can only be made by the FDA as the Agency is tasked enforcing the requirement found in a given USP monograph.

98. Dr. Najafi concludes, "Valsartan containing products that contained NDMA and NDEA were not the generic equivalent of Diovan or Exforge because they contained NDMA and NDEA."

99. As presented above, Valsartan manufactured by a different route of synthesis that resulted in a different impurity profile still would be considered the same as that used in the RLD.

100. By the same token, a generic drug that contains impurities or inactive ingredients that are different than those found in the RLD does not mean the generic drug is not bioequivalent. Per Section 505(j)(8)(B) of the FDCA, bioequivalence is a separate concept relating to the absence of a significant difference in the rate and extent to which the API becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

101. Further, even assuming their presence in the form of process impurities, NDMA and NDEA would not be considered active ingredients in a drug product because they are not a component that is "intended to furnish pharmacological activity or other direct effect in the

diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals," per 21 CFR 210.3(b)(7).

102. Moreover, FDA's establishment of specifications and standards in mid-to-late 2018 for nitrosamine content does not retroactively render all previously manufactured drug substance or drug product adulterated or misbranded.

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/s/ Eric Sheinin
Eric Sheinin